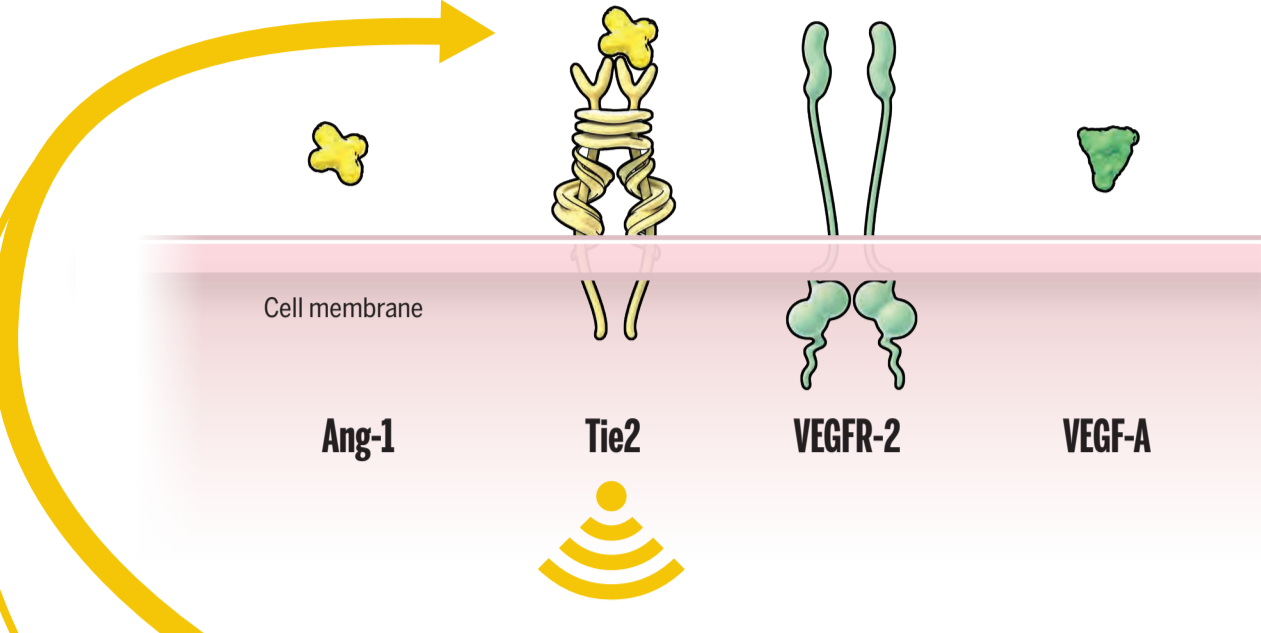


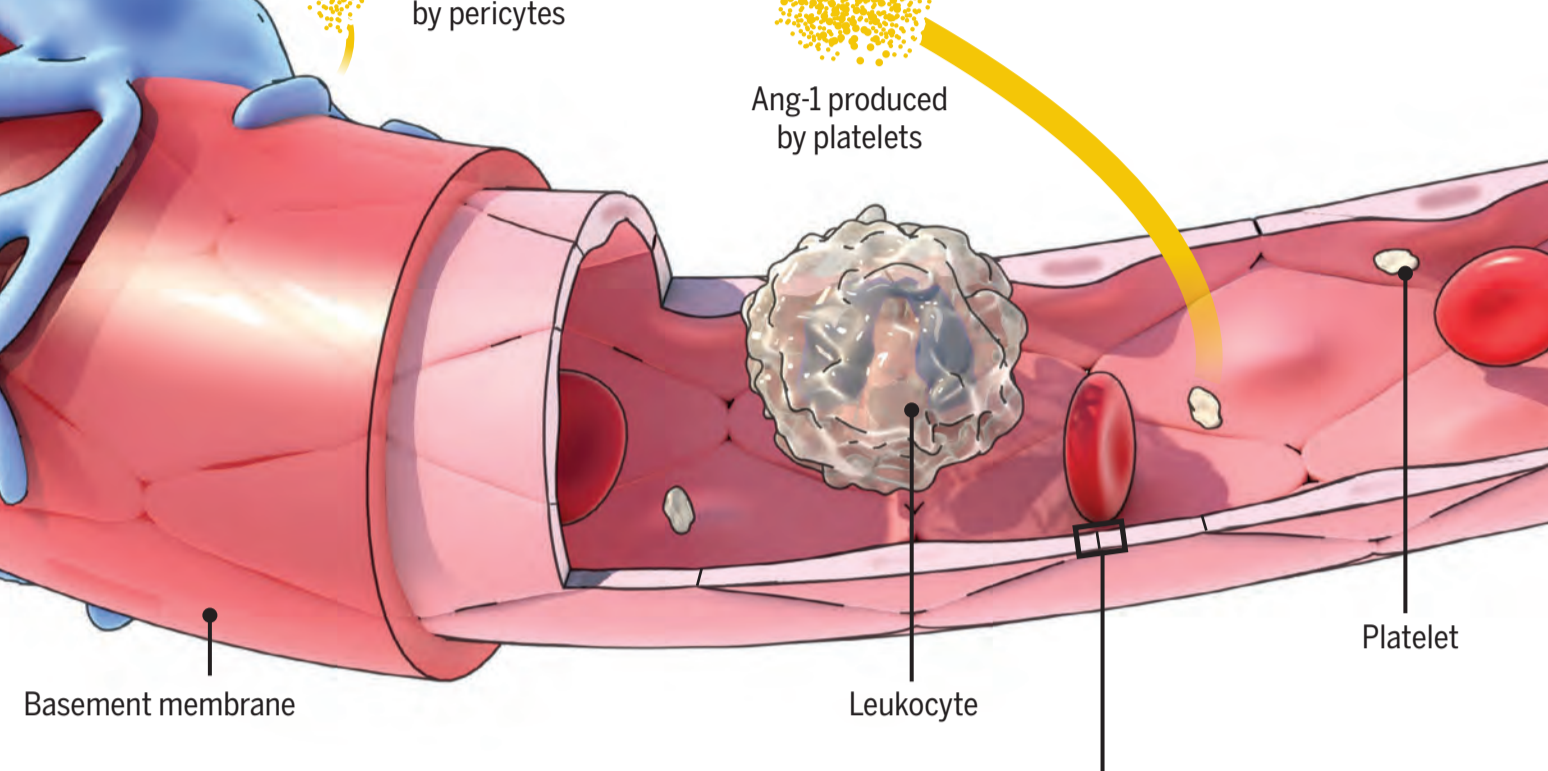
Angiopoietins: Key Regulators of Vascular Stability

Ang-1 Promotes Vascular Stability to Maintain Healthy Vessels

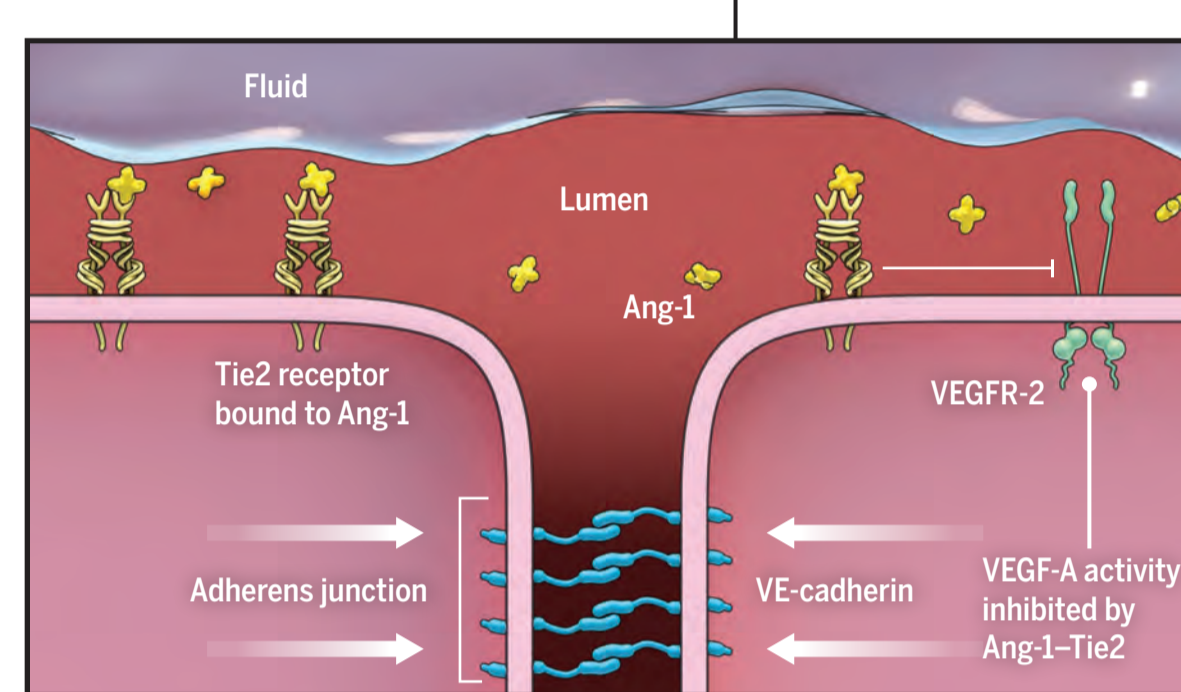
1 Ang-1 Binds to and Activates Tie2...
Ang-1 is made by platelets and pericytes and activates Tie2 receptors on endothelial cells to maintain vascular stability.



2 ...Tightening Endothelial Cell Junctions

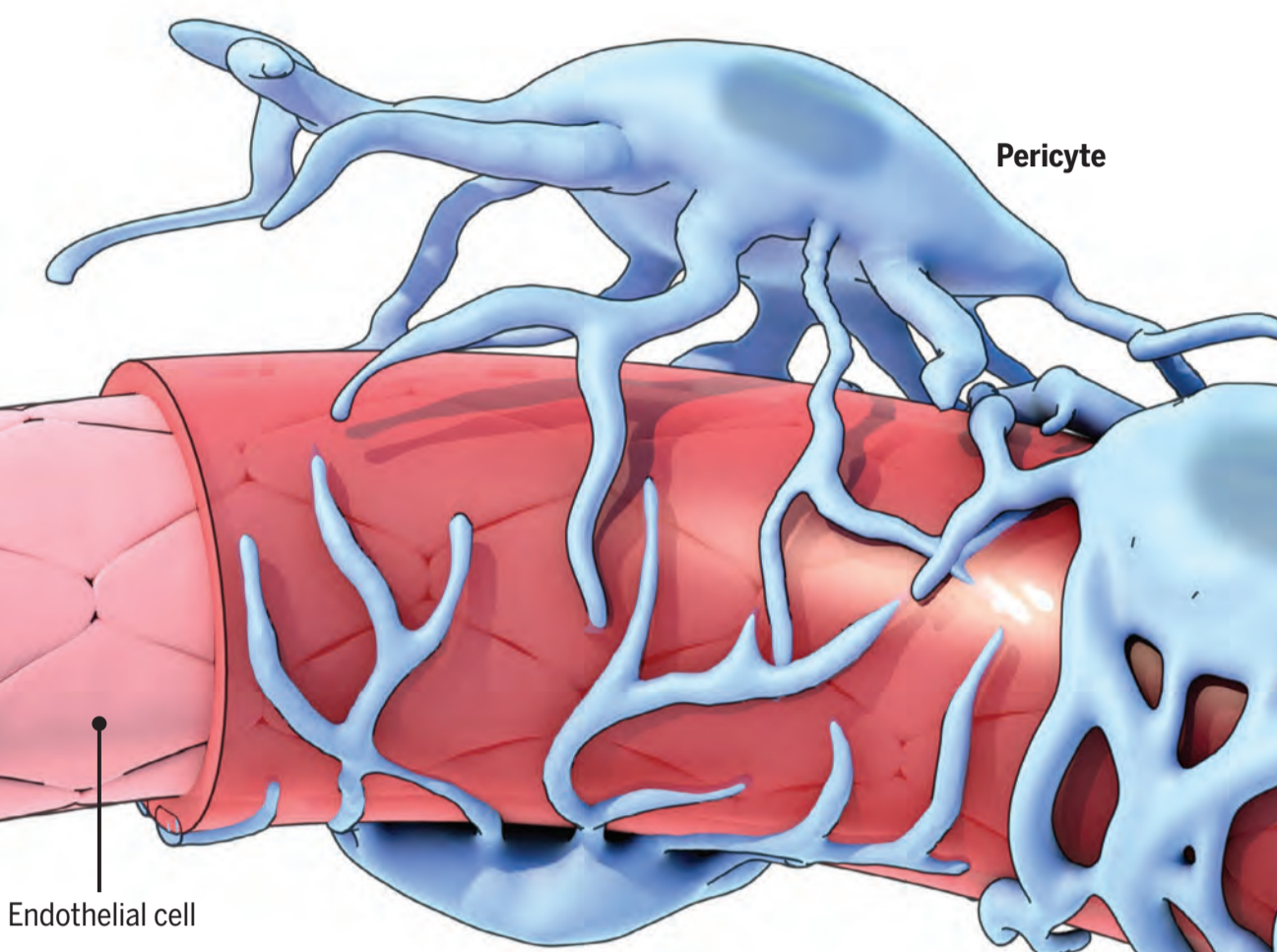


Tightened cell-cell junctions prevent vascular leakage at the blood-retina barrier.

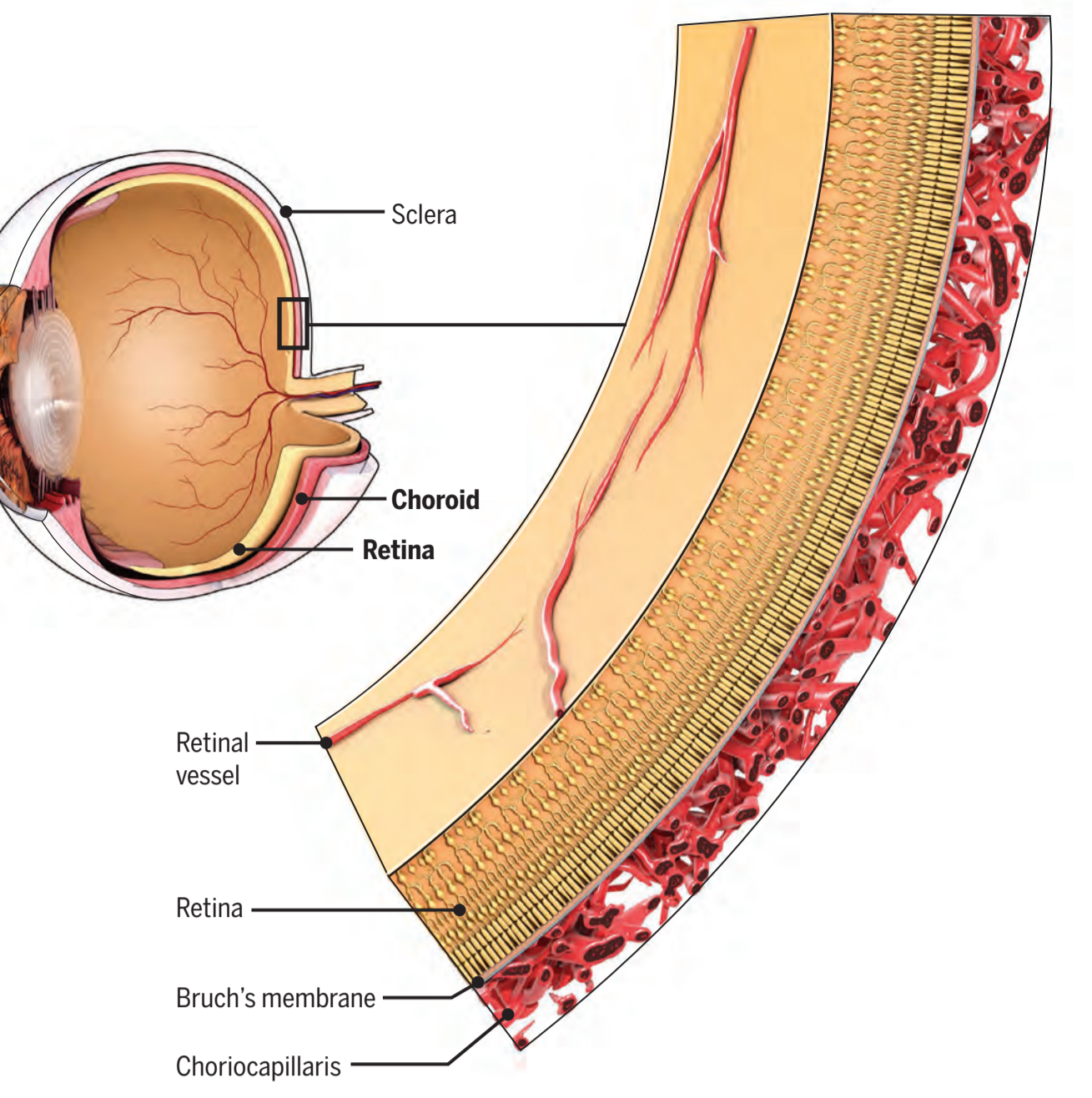
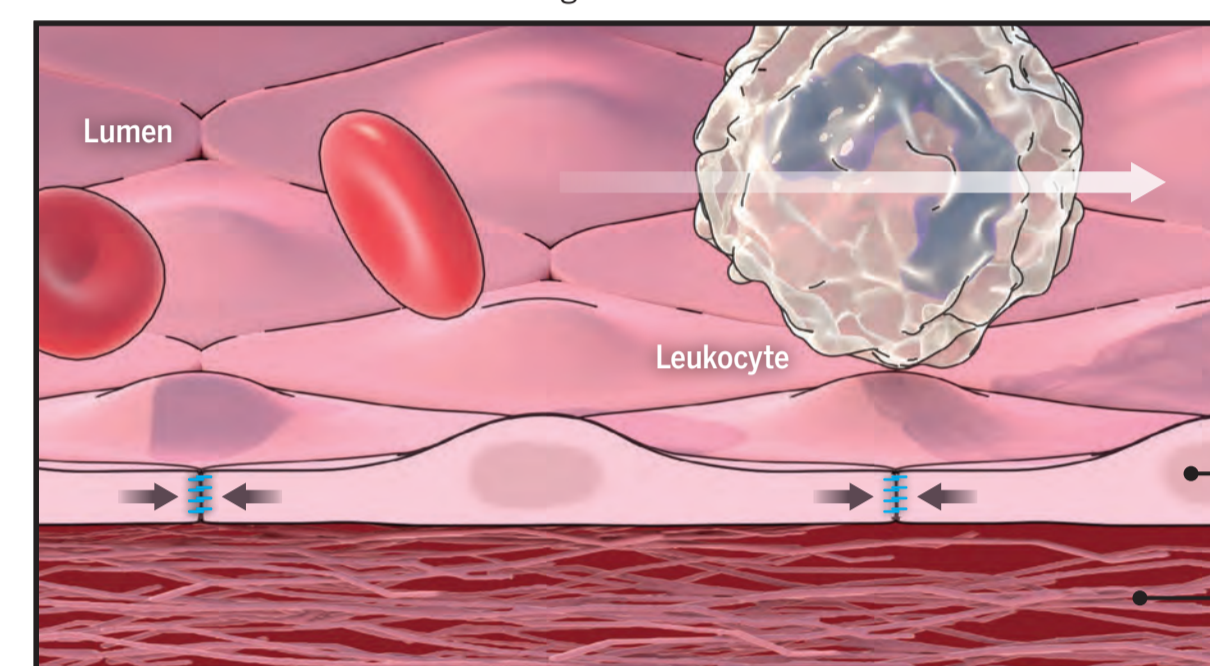


Weak VEGF-A Responsiveness
Ang-1-Tie2 signaling downregulates VEGFR-2 and prevents neovascularization.

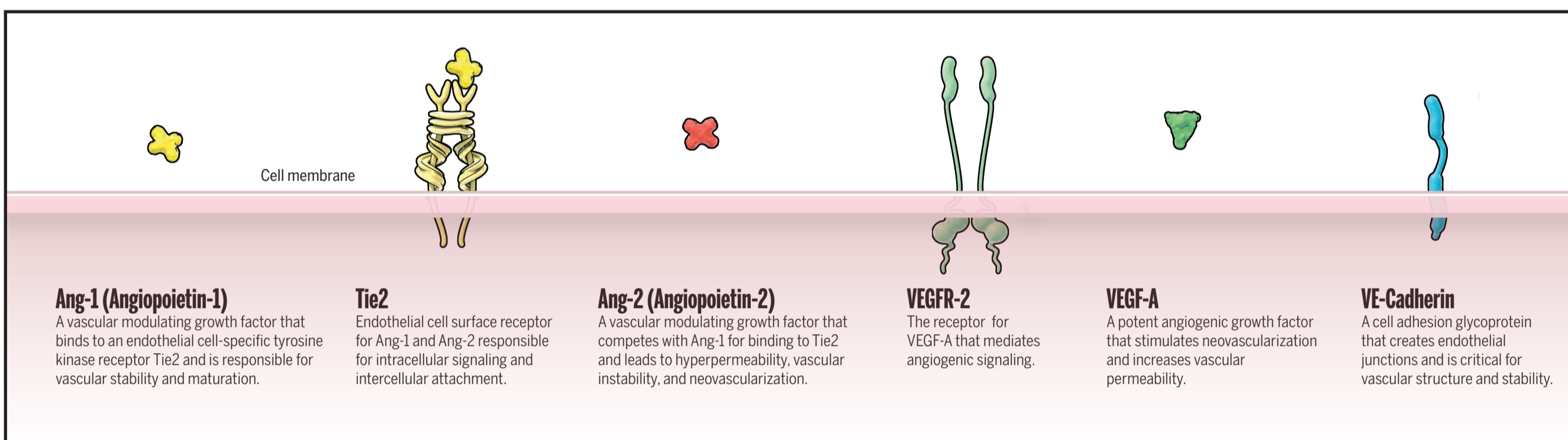
3 Pericytes are Recruited for Vascular Stability and Maturation
As perivascular cells wrap around vessels, they inhibit endothelial proliferation and further reduce vascular leakage.



In healthy blood vessels, leukocytes flow through the bloodstream but do not adhere to vessel walls or transigrate into the extracellular matrix.

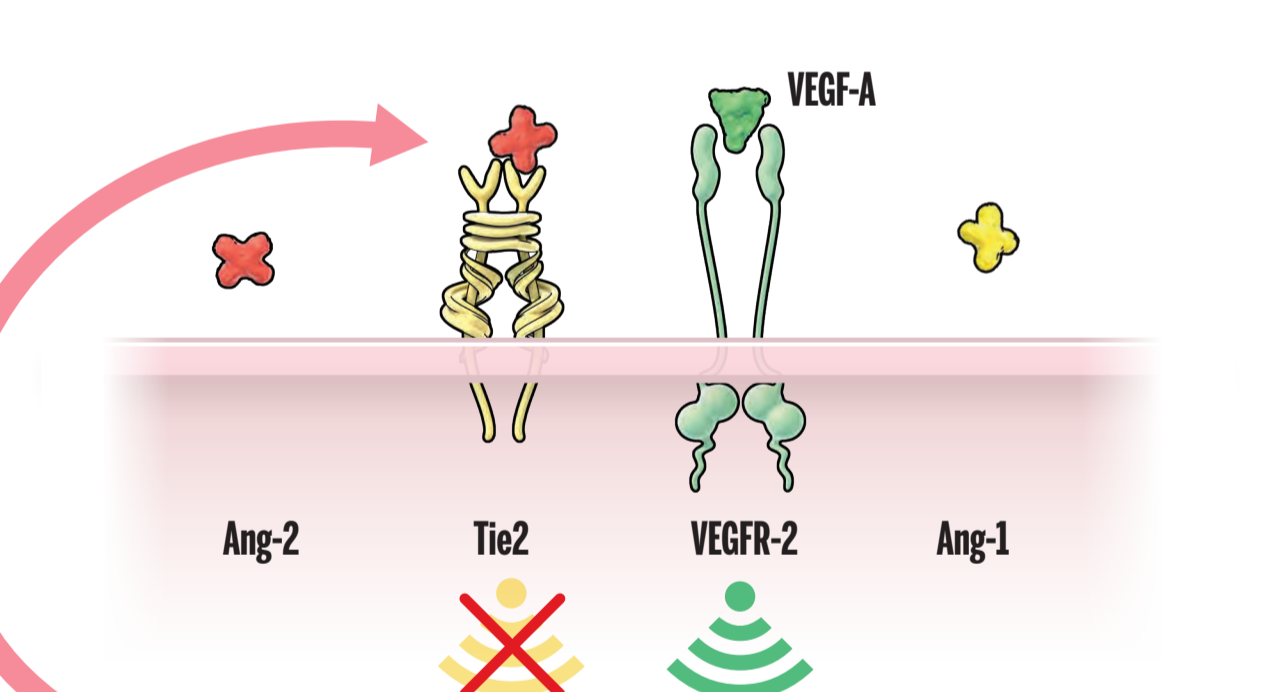


4 Resulting in Endothelial Quiescence and Homeostasis
Constitutive Ang-1-Tie2 signaling is critical for maintaining the non-proliferative, anti-inflammatory and non-angiogenic state of the healthy blood vessel.

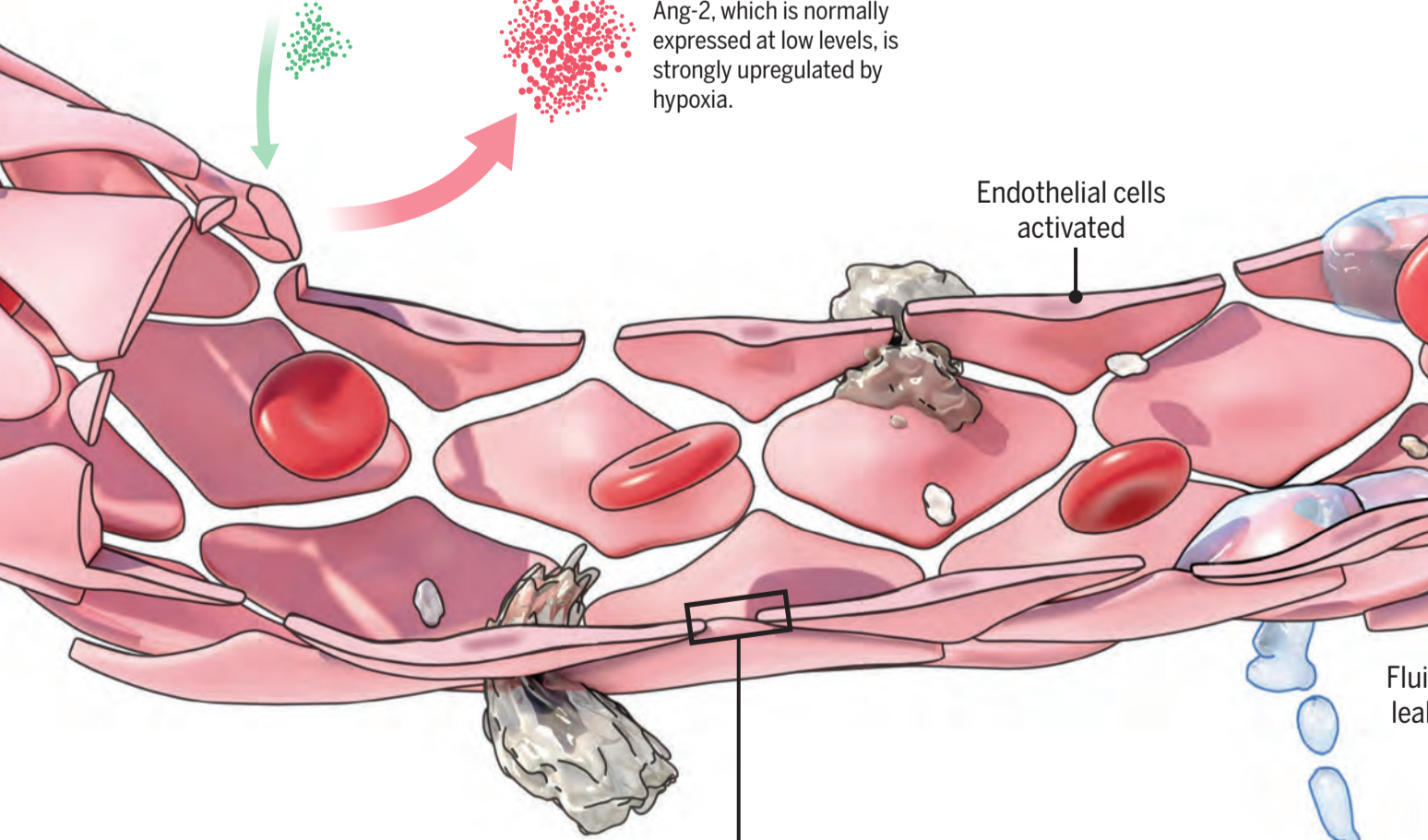


Ang-2 Promotes Vascular Instability in Disease by Blocking Ang-1-Tie2

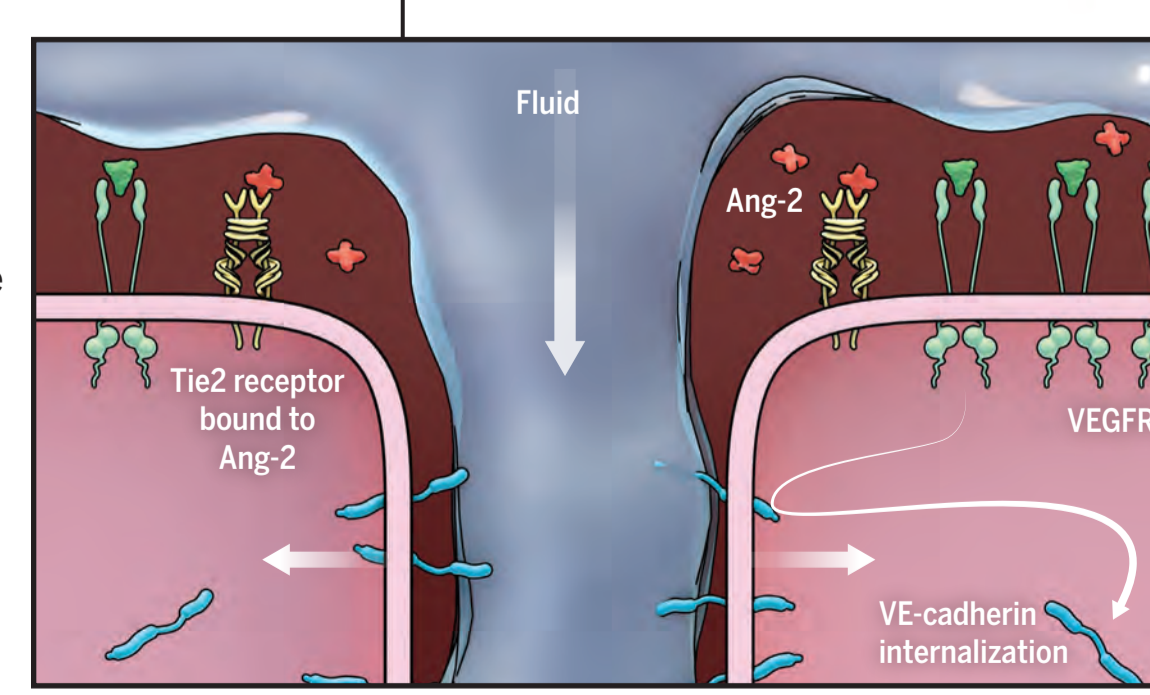
1 In Diseases, Upregulated Ang-2 Binds to and Blocks Tie2 Signaling ...
Elevated Ang-2 competitively disrupts Ang-1-Tie2 activation.



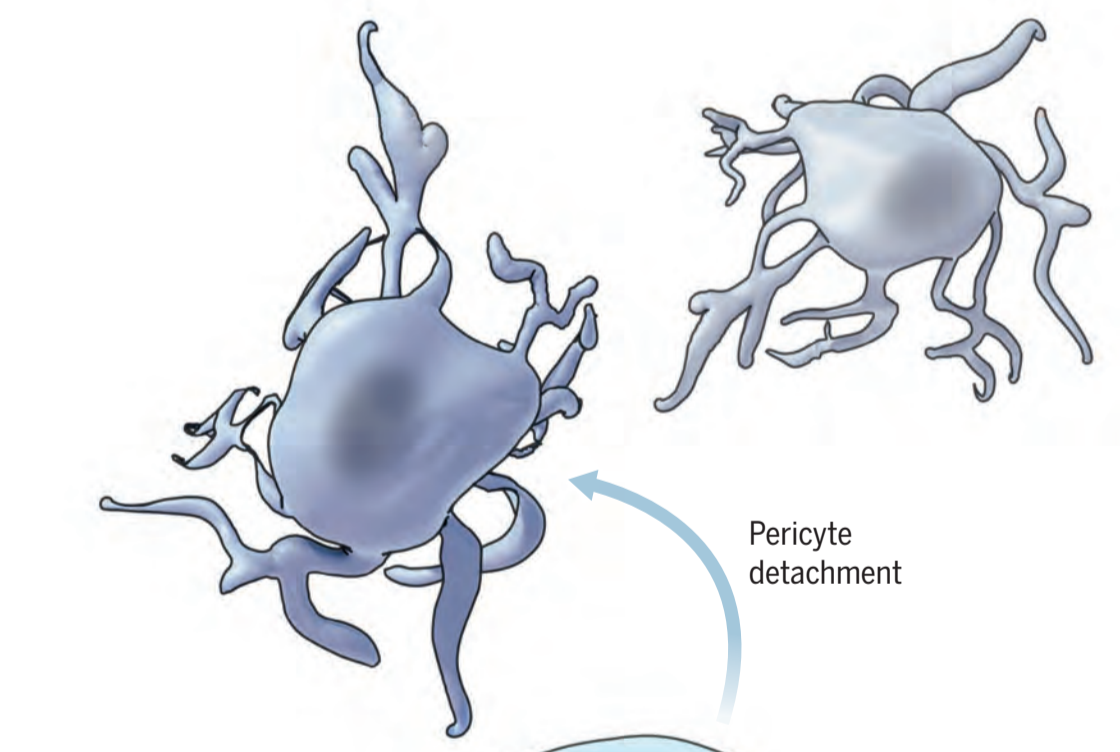
2 ... Leading to Loosening of Endothelial Tight Junctions and Vascular Leakage



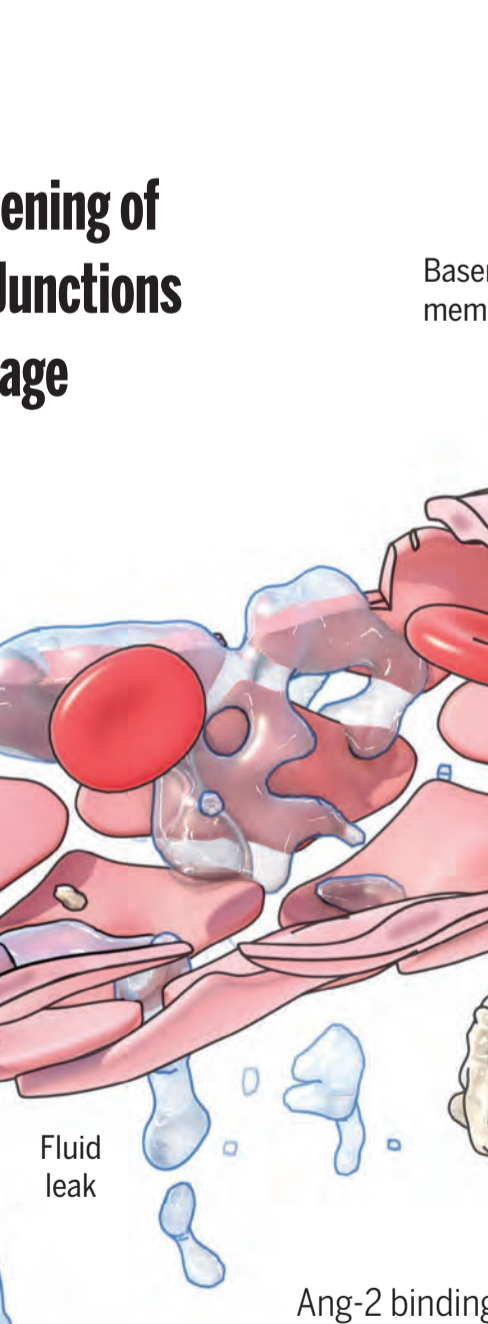
Prevention of Tie2 signaling by Ang-2 leads to a breakdown of endothelial tight junctions, and upregulated VEGFR-2 expression, amplifying the vascular response to VEGF-A.



4 Upregulated Ang-2 Leads to Pericyte Drop Out and Loss, Destabilizing Vessels
Pericytes detach and further destabilize vessels which prepares them to initiate neovascularization, and exacerbates leakage.

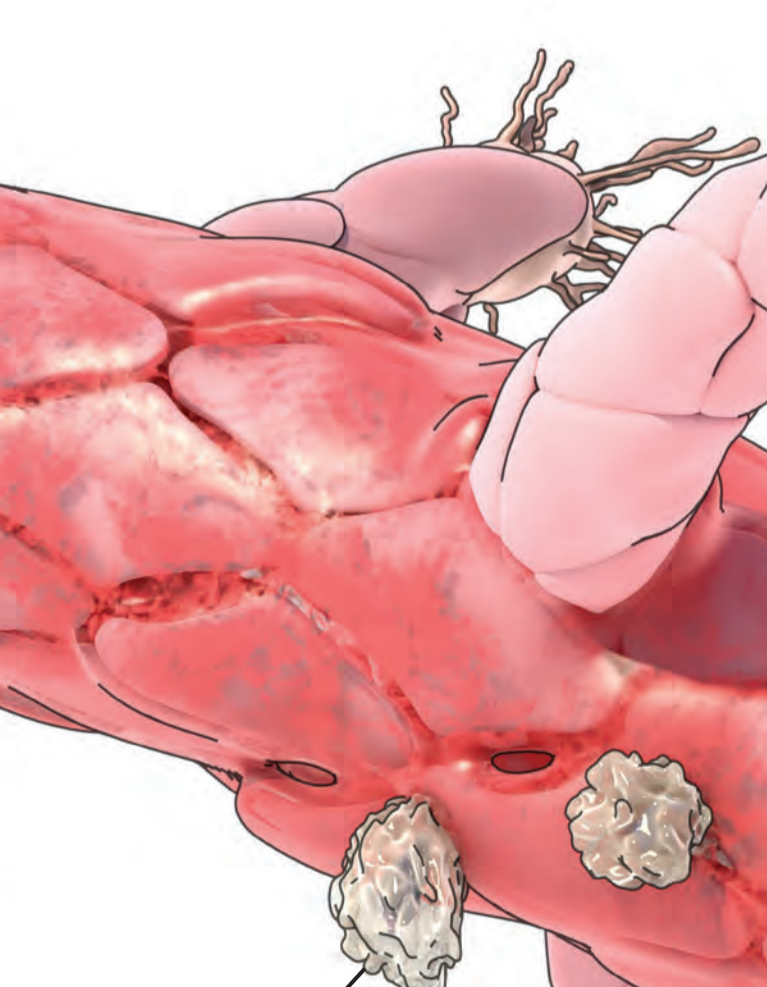


3 ... and Increased Inflammation



Ang-2 binding to Tie2 leads to expression of adhesion molecules which allows leukocytes to attach to vessel walls and migrate out through widened cellular gaps into surrounding tissue.

5 Vascular Sprouting and Neovascularization Occurs ...
Ang-2 binding to Tie2 results in increased expression of VEGFR-2, leading to greater responsiveness to VEGF-A, potentiating neovascularization.



6 ...Leading to the Progression of Choroidal and Retinal Vascular Diseases
Together VEGF-A and Ang-2 play a critical role in the development of retinal diseases.

